COMPARISION OF
INSULIN AND GLIBENCLAMIDE
IN GESTATIONAL DIABETES MELLITUS

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BONAFIDE CERTIFICATE

This is to certify that the Dissertation entitled **"COMPARISON OF INSULIN AND GLIBENCLAMIDE IN GESTATIONAL DIABETES MELLITUS"** is a bonafide work of **Dr K. ABIRAMAVALLI,** Roll No: 20031551, who carried out the Dissertation under my supervision. Certified further that to the best of my knowledge, the work reported hear in does not form part of any other thesis or Dissertation on the basis of which a degree or award was conferred on an earlier occasion on this or any other candidate.

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CONTENTS

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CHAPTER - 1
INTRODUCTION

Diabetes Mellitus complicates 2–20% of all pregnancies. Of this 90% is Gestational diabetes mellitus.

Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy regardless of whether or not insulin is used for treatment.

Hyperglycemia is associated with adverse outcomes of pregnancy in women with Gestational diabetes mellitus. The principal approach to glycaemic control in pregnant women with diabetes is dietary therapy and insulin administration has been standard therapy for dietary failures until recent years. Approximately 30 – 40 % of patients require pharmacological treatment. Antihyperglycaemic drugs were not used during pregnancy for fear of neonatal hypoglycaemia and foetal anomalies. This is based mainly on studies before the availability of drugs like Glibenclamide and Glipizide, which are in common use today. Studies have demonstrated that glibenclamide does not cross human placenta in appreciable quantities, in contrast to older sulfonylurea drugs and metformin. Insulin therapy has the disadvantages of patient discomfort, inconvenience of injections and expense

there by potentially compromising compliance.

On the basis of these findings and the relatively mild hyperglycaemia in most pregnant women with Gestational diabetes mellitus, Glibenclamide might be an alternative therapy in patients with Gestational diabetes mellitus.

CHAPTER – 2

REVIEW OF LITERATURE

HISTORY

Diabetes was described more than 2000 years ago. An ancient Hindu document by susruta in India in about 400 BC has described the Diabetic syndrome as characterized by a “honeyed urine”. The word Diabetes (to flow through) was coined by Greek physician Aretaus of Cappadocia in first century (150 AD) from the word siphon (sweet taste). The word mellitus (honeyed) added by John Rollo in 18th century. In 1674 Thomas Willis, a physician, anatomist and a professor of Natural Philosophy at oxford discovered by tasting that the urine of diabetic persons was “Wonderfully sweet as if imbued with honey or sugar”. Willis could not explain the chemical nature of this sweet substance. It was Mathew Dobson of Manchester, England who in 1776 demonstrated that diabetics actually excrete sugar in urine. It was John Rollo, Surgeon general of Royal artillery who first applied the discovery of glycosuria by Dobson to the quantitative metabolic study of diabetes. The entity gestational diabetes mellitus was firmly established in 1964 (O’Sullivan and Mahan).

It was Claude Bernard who studied the association between pancreas and diabetes. The name Insulin was christened by De Mayer (1909). In 1921 Fredrick Banting and Charles Best with the help of chemist J B Collip succeeded in fulfilling all of the criteria for therapeutic active Insulin. The name insulin is derived from the Latin word “INSULA” which means “AN ISLAND” denoting the beta cells of Islets of Langerhans. Insulin was isolated in crystalline form by Abet in 1938. Sanger elucidated the chemical structure of insulin in 1960. Insulin molecules were fully synthesized in lab by 1996.

In the pre-insulin era pregnancy in the diabetic women cannot even be dreamt of. The maternal mortality ranged from 6 to 45% before 1921. Even after the introduction of insulin in the treatment of diabetes in pregnancy the perinatal mortality remained near 30%. During 1940 to 1970 the perinatal mortality was brought down to 20% by comprehensive team approach by obstetrician, diabetologist, neonatalogist and anaesthetist. With the introduction of AN foetal surveillance between 1971 to 1976 the perinatal mortality was reduced to 12%.

OHA IN PREGNANCY

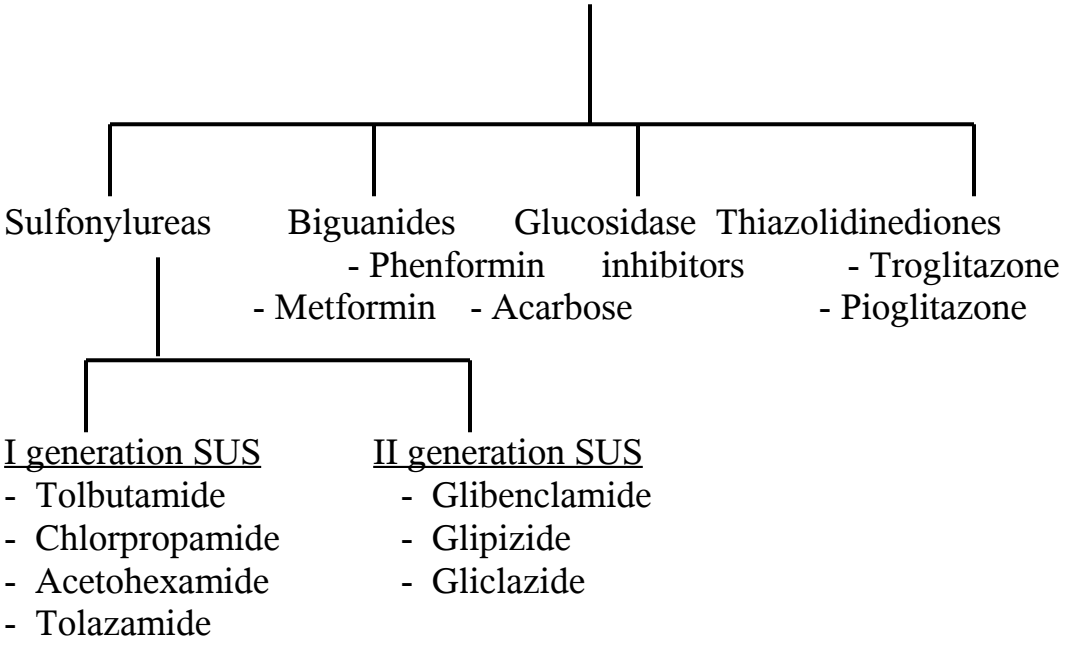
The Hypoglycaemic action of Sulfonylurea was an accidental discovery during the end of world war-II, while treating typhoid fever. The first OHA suitable for clinical use, the Sulfonylureas developed by Auguste Loubatieres in early 1940's. In 1961 Endean and Smith thought that the treatment of diabetes with oral agents had been a tremendous step forward and advocated its use in diabetic women. Jackson et al started a storm with their report of 42 women who received tolbutamide or chlorpropamide during pregnancy. He concluded that chlorpropamide in a dosage of 500 mg /day appeared to be associated with a high perinatal mortality, although it might be safer at a lower dosage and that tolbutamide appeared to be safe. This high perinatal mortality may be due to poor diabetic control rather than due to congenital anomalies.

Langer et al 2002 stated OHA in pregnancy – "Their time has come". (Journal of maternal, foetal and Neonatal medicine – 2002). Use of Glibenclamide in pregnancy is considered to be safe in pregnancy because of insignificant placental transfer of it in humans by using in vitro models such as placental perfusion models, leading to successful clinical trial of glibenclamide (Garcia –Bournissen, clinical pharmacokinectics-2003).

Recently Gabbe and Graves stated, “an alternative to insulin therapy is the oral hypoglycaemic agent – glyburide”. (AJOG – 2005).

There are limited data on exposure of OHA’S to the infant via breast milk, and the serious effect of neonatal hypoglycaemia, the safest recommendation is not to breast feed the infant while taking OHA. (AU Merlob P levitt O Stahl B-SO Pediatric drugs – 2002) but glibenclamide is not secreted in breast milk (Diabetes care Feb-2006).

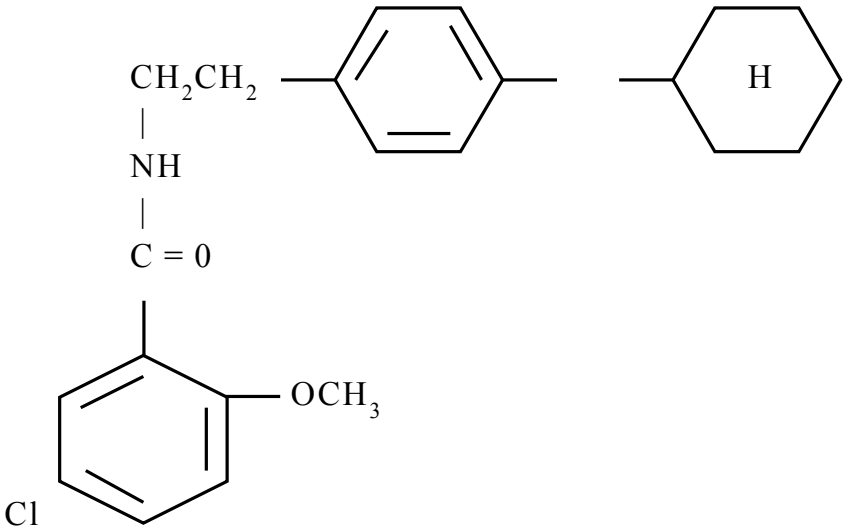
Classification of oral Hypoglycamic agents



GLIBENCLAMIDE – PHARMACOLOGY

It was the first “second generation” Sulfonylurea to be introduced in clinical practice and it is the most potent’

CHEMICAL STRUCTURE OF GLIBEMCLAMIDE



MECHANISM OF ACTION

1. Stimulation of insulin release from the pancreas –single dose provokes brisk release of insulin from pancreas. Glibenclamide acts on the sulfonylurea receptors on the pancreatic beta cell membrane – causes depolarization by reducing conductance of ATP sensitive potassium channels. This enchances calcium influx – degranulation. The rate of insulin secretion at any glucose concentration is increased.

2. Reduction of glucagon levels.

3. Increasing somatostatin release.

4. Hepatic degradation of insulin is slowed.

5. It has a extrapancreatic action. It increases binding of insulin to target tissues and receptors.

PHARMACOKINETICS

Glibenclamide when given orally is absorbed well but slowly than the micronised form. Although concomitant food intake does not seem to delay the absorption its efficacy is increased if given before food. It has very low volume of distribution (0.2-0.42/Kg) and it is very extensively bound to albumin (90%-95%). Glibenclamide is completely metabolized mainly by oxidation to two hydroxylated metabolites both of which have glucose reducing activity. About half of a given dose of glibenclamide is eliminated by renal excretion of metabolites and a significant portion is excreted through the bile. Although renal insufficiency does not alter the elimination rate there is risk of hypoglycaemia. This is because renal insufficiency is associated with reduced drug binding to albumin in addition renal impairment may lead

to accumulation of polar, active metabolites. It has relatively short half life (4-9 hrs). There is insignificant transfer of glibenclamide through the human placenta due to its property of high plasma protein binding and short half life. Moreover glibenclamide is a substrate for P-glycoprotein which is extruding pump in the placenta and inhibits it, thus preventing transplacental transfer of the drug in humans. Usual dose is 1.75 – 14.0 mg (micronised) or 2.5 – 20.0 mg (non-micronised) per day.

The main concern about glibenclamide is its drug interactions. Hypoglycaemia, Nausea, Vomiting, diarrhoea, Hypersensitivity reactions are some of the adverse effects of glibenclamide. Incidence of adverse effects is quite low (3-7 %).

SCREENING FOR GDM

Screening of GDM should be universal as GDM is mostly asymptomatic. In a study by Hughes et al 1995 found that selective screening would have failed to detect 43 % of gestational diabetes mellitus. 28 % of them would have required Insulin.

O'SULLIVAN'S ORAL GLUCOSE CHALLENGE TEST [OGCT]

It is otherwise known as universal screening test of O'Sullivan. This consists of giving a 50 gm glucose load irrespective of the patient's feeding state and estimating plasma glucose after 1 hour and a value of > 140 mgm / 100 ml is taken as the cutoff. In 1990 Chicago workshop conference on gestational diabetes recommended that all pregnant women should be screened [Universal Screening] using a 50 gms. Oral glucose challenge test between 24 and 28 weeks without regard to the time of day or last meal and that a plasma value at 1 hour exceeding 140 mgm/dl be used as cut-off for performing the diagnostic 100 gms 3 hrs oral glucose tolerance tests.

Sacks and Colleague (1976) studied on the reproducibility of this standard test and concluded that this reproducibility is adequate. This procedure involves the patient waiting for 1 hour following glucose ingestion and positive screenee have to have a second glucose load for diagnosis and it is also costly.

O'SULLIVAN& MAHAN'S ORAL GLUCOSE TOLERANCE TEST [OGTT]

This test serves as the Gold standard for the diagnosis of gestational diabetes mellitus. In O'Sullivan's studies, whole blood was tested using the Somogyi – Nelson method for measuring reducing substances. Plasma Glucose values have been shown to be 14% higher than those in whole blood obtained from the same sample using the same assay method. Hence, NDDG adopted O'Sullivan's values to plasma glucose. Later NDDG reinterpreted O'Sullivan's data for glucose oxidase method on plasma by increasing O'Sullivan criteria by 15%. This criteria reaffirmed by American Diabetic Association in 1985, stated that the glucose oxidase method is specific for glucose and generally result in 5 mg / dl decrease in measured values in the range of glucose concentration (Carpenter and coustan).

The upper limits for normal (threshold) were selected statistically and defined as two standard deviation (SD) above the mean for each of the four glucose values in 3hr test. The gestational diabetes mellitus is diagnosed when two values meet or exceed the threshold. If one value is abnormal, it is called single value abnormality and if the 2hr value is above 120mg % it is diagnosed as Impaired Gestational Glucose Tolerance.

Patient in high-risk group should have a glucose tolerance test done, as early in pregnancy as possible and if they have a normal glucose tolerance curve, the test should be repeated at 28 weeks gestation. At this gestational age, diabetogenic effect of pregnancy is near its peak and the chances of a positive result from glucose tolerance test are high.

Because O'Sullivan's original criteria were developed from statistical model it remains uncertain whether even the most accurate transliteration of them to modern testing method is relevant.

CRITERIA FOR DIAGNOSIS

Time	O'Sullivan (48) and Mahan	NDDG (49) Adaptation	Carpenter and (50) Coustan Adaptation
Fasting	90	105	95
1 hour	165	190	180
2 hour	145	165	155
3 hour	125	145	140

75 GM ORAL GLUCOSE TOLERANCE TEST

1. Gestational diabetes mellitus diagnosis based on 2 hr 75 gm oral glucose tolerance test defined by either WHO or ADA predicts adverse pregnancy outcome.

2. The criteria recommended by WHO is simple and cost effective and practiced by many centers.

3. Further assuming that effective treatment is available, WHO criteria of 2 hr plasma glucose greater than or equal to 140mg/dl identifying a large number of cases may have a greater potential for prevention.

4. One step procedure of WHO (2 hr PPG greater than or equal to 140 mg/dl) serves dual purpose of both screening and diagnosis.

Seshiah et al stated that diagnosis of GDM by OGTT based on initial glucose challenge test screening leaves 21.5% undiagnosed. The two step procedure. Glucose challenge test followed by glucose tolerance test is not practical, as patients have to visit the clinic at least twice. Hence glucose challenge test with 75 gm of oral glucose load and diagnosing GDM if the 2 hr plasma glucose is greater than or equal to 140mg/dl as recommended by WHO would be more practical. (The journal of obstetrics and gynecology of India 2005).

GLYCOSYLATED HAEMOGLOBIN

Second generation tests came into vogue since 1970's and they had the advantage of high lighting on past glycaemic control. Glycosylated Haemoglobin was used as a screening test during 1970's. The chemical reaction referred as glycation describes the linkage between a reducing sugar and a receptive amino acid. Mailard first described this in relation to food protein in 1912. Its possible relevance to clinical diabetes mellitus was recognized in 1962 when Huisman and Dozy observed that HbA1, which is the glycosylated fraction of glycosylated Haemoglobin, was increased in diabetics. In the diabetes mellitus the level of HbA1c would be proportional to the integrated blood glucose levels in the previous 7-8 weeks period approximating to the half – life of the average red blood cell shown by Gabbet et al in 1977.

Estimation of HbA1C is the measure of average and cumulative control of glycaemia of previous two to three months. It may be useful only in the retrospective documentation of GDM.

GDM however may not present with the constant elevation of blood glucose level as in non-pregnant state. Gravid women with GDM have low fasting

blood glucose concentration, increased erythropoesis, younger RBCs, less glycated Hb., and fluctuating blood glucose level due to rapid change in the hormonal milieu. Hence as the measure of chronic hyperglycemia, HbA1c may not be so effective in the diagnosis of gestational diabetes mellitus.

Shah et al. measured HbA1c using exchange chromatography and applied NDDG criteria for gestational diabetes mellitus in a group of patients with risk factors. In the risk group, HbA1c level > 8.8% taken as abnormal. The results showed 27 % sensitivity for glycated Hb in the identification of gestational diabetes mellitus, these data do not support the use of HbA1c as a screening test for gestational diabetes mellitus.

It cannot be used for day-to-day adjustment of control [Irwin] and it cannot register hypoglycemia [Irwin]. It has poor sensitivity at lower blood glucose levels and it is not discriminative enough to differentiate between mean blood glucose of 90 and 135-mgm %. Hence not very useful in monitoring the control of gestational diabetes mellitus [Donald R Couston]. It can supplement but not replace blood glucose as accurately as in non-pregnant state. [Gam Su H.R]. Hyperglycaemia that affects HbA1c needs to be long standing while the hyperglycaemia that affects pregnancy develops in second trimester (Jovanoic et al). It is expensive and the results are disappointing

(Oats et al 1987). HbA1c is most useful in pre-pregnancy clinic for counseling and also to predict foetal outcome.

The other glycosylated plasma proteins have the potential, as markers for gestational diabetes mellitus. Among them the glycosylated albumin has a shorter half-life than that of HbA1c and may be more effective in identifying women with an acute rise in mean daily blood glucose.

METABOLIC CHANGES IN NORMAL PREGNANCY

The fuel metabolism during normal pregnancy is characterized by

- Facilitated insulin action during the first half of pregnancy and
- Diabetogenic stress during the second half of pregnancy.

EARLY WEEKS OF GESTATION

In the early weeks of gestation certain hormonal changes occur.

- Increase in fasting insulin concentration
- Increase in glucose stimulated insulin release which reaches a peak at 18-20weeks.
- Increase in serum levels of estrogen and progesterone which induces beta cell hyperplasia.

During the earlier weeks of gestation (before 20weeks) foetal requirements for glucose is minimal.Hence in the normal pregnancy steroid stimulated insulin secretion can promote increased peripheral utilization of glucose.

Excess of glucose available in the fed state is converted to fatty acids and stored in adipose tissue and glucose carbon is used for protein synthesis. This is the anabolic phase of pregnancy when the mother stores energy in the form of tissue glycogen and fat stores.

By the mid and late trimester accelerated maternal insulin and enhanced peripheral utilization of glucose leads to hypoglycaemia in fasted stated. This hypoglycaemia will lower the insulin secretion and enchances the hydrolysis of fat for release of fatty acids as alternate fuels. These net effect is called “Accelerated starvation” characterized by hypoglycaemia ,hyperketonemia and protein catabolism.

CARBOHYDRATE METABOLISM IN EARLY PREGNANCY (TO 20 WEEKS)

Hormonal alteration	Effect	Metabolic Change
↑ Estrogen and ↑ Progesterone ↓ B-cell Hyperplasia and ↑ Insulin Secretion	↑ Tissue Glycogen storage ↓ Hepatic glucose production ↑ Peripheral utilization of glucose ↓ Fasting Plasma glucose	Anabolic ↑ Due to sex steroids + Hyper insulinemia

LATER WEEKS OF GESTATION

In the later part of pregnancy (from 20 weeks) foetal growth is much more rapid and there is increased nutrient flow across the placenta. The foetus competes with the mother for circulating glucose supplies. The insulin resistance and anti-insulin hormones helps to maintain glucose concentration and adequate glucose supply to the foetus. Thus glucose in the maternal circulation is diverted to the foetus.

The mechanism behind this altered metabolism is due to counter insulin hormones elaborated by the placenta. These are as follows.

1. Human chorionic somatomammotrophin (HPL) is the major peptide elaborated by the placenta. It has insulinotrophic and lipolytic properties. HPL inhibits glucose utilization by the mother and promotes glucose transfer to the foetus, thus maintaining the balance of accelerated foetal

growth.

2. Placental insulinase and insulin antibodies may play a role as counter insulins.

3. In addition there is elevated levels of prolactin, Cortisol and glucagon concentration in late pregnancy which also confers insulin resistance.

These events occur in the catabolic phase of pregnancy. Due to lipolytic action of HPL the mother uses fat as alternative fuel diverting glucose for foetal utilization. During the fasted state amount of fat are drawn from adipose tissue store. This accelerated fat metabolism during fasted state leads to ketoacidosis Hence pregnant women are strictly instructed not to be in a fasted state.

CARBOHYDRATE METABOLISM IN LATE PREGNANCY

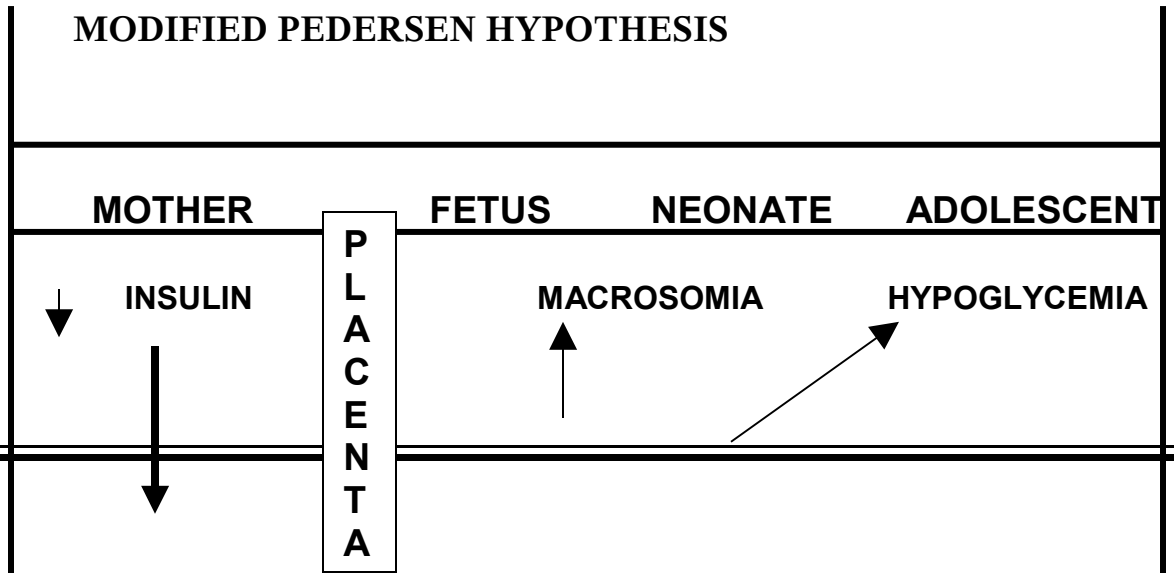
Hormonal alteration	Effect	Metabolic Change
↑ H C S	"Diabetogenic"	Facilitated

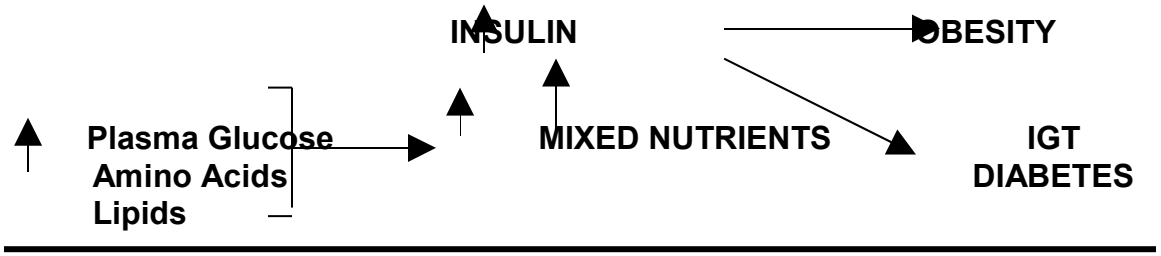
↑ Prolactin ↑ Bound and free cortisol	↓ Glucose tolerance Insulin resistance ↓ Hepatic glucose stores ↑ Hepatic glucose production	Anabolism during feeding Accelerated starvation during fasting ↓ Ensures glucose and AA to fetus.

ALTERED METABOLISM IN DIABETIC PREGNANCY

The transport of maternal fuel to the foetus requires normal placental intermediary metabolism and normal supply of substrates. Because diabetes may result in markedly abnormal concentrations of maternal glucose, fatty acids, triglycerides and amino acids, these may get transported to the foetus. Unlike the foetus of early gestation, the foetus of the late gestation is well equipped to synthesise and replace insulin from its pancreas and protect itself against brunt of abnormal fuel mixture, thereby normalizing blood sugar in circulation but in the process resulting in hyperinsulinemia of the foetus and due to its anabolic action causes macrosomia and associated complications.

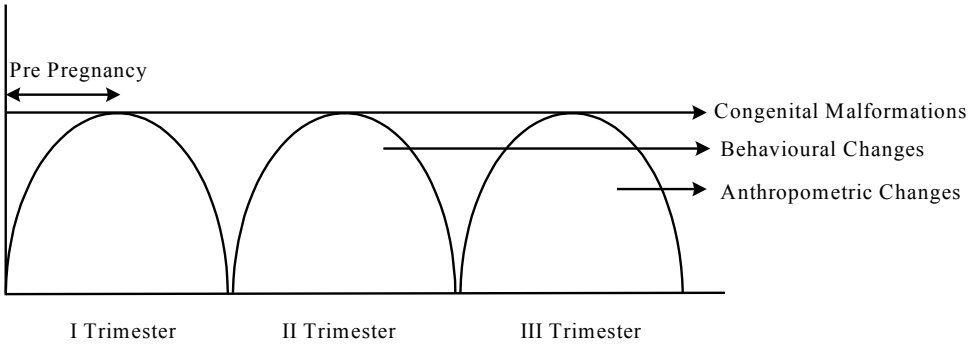
MODIFIED PEDERSEN HYPOTHESIS





Gestational carbohydrate intolerance is asymptomatic. The subjects destined to develop gestational diabetes mellitus have limited pancreatic insulin reserve and reduced insulin sensitivity. The stress of pregnancy due to counter insulin hormones overwhelms the insulin reserves hence in the plasma, levels of all classes of fuels – aminoacids, fatty acids and glucose are elevated which are delivered to the foetus. This change is seen more during the latter half of pregnancy when counter insulin factors and insulin resistance is experienced. The foetal transportation of abnormal fuels result in hyperinsulinemia and the resultant macrosomia. Thus macrosomia and associated risk factors like prematurity, traumatic delivery, RDS, neonatal hypoglycaemia, hypocalcaemia, hyperbilirubinemia become the major concern for the subjects with gestational diabetes.

FREINKELS FUEL MEDIATED TERATOGENESIS



EFFECTS OF GDM ON THE MOTHER AND THE FOETUS

ON THE MOTHER

- Pre-eclampsia and pregnancy induced hypertension is seen in 13.7% in gestational diabetes. Combs et al and Rosenn et al reported a significant association between poor glycaemic control and pre-eclampsia or pregnancy induced hypertension. The incidence of chronic hyperetension is 2.5% among gestational diabetes.

- Overall incidence of ketocidosis is 0.7% especially following beta agonist therapy. Kilvert et. Al; reported one case of diabetic ketoacidosis in 150 cases of gestational diabetes mellitus. Diabetic ketoacidosis is preventable

and the prevention can be accomplished with optimal gycaemic control.

- The incidence of Hydraminos ranges from 2.0 to 2.1% in gestational diabetes mellitus and it is about 20% to 30% in overt diabetics. Most infants of hydramniotic diabetic pregnancy are structurally normal, associated with increased incindence of preterm labour and premature rupture of membrane.

- Pyelonephriris was reported in 1.2% of gestational diabetes mellitus and 3.6% overt diabetes. There is no difference in incidence of Pyelonephritis in gestational diabetes mellitus and control groups.

- Preterm labour complicated 8.1% of gestational diabetes. There is a significant correlation between preterm labour and uro-genital infection. (Candida and Trichomoniasis). Molsted and Pederson speculated that, hormonal differences increased the frequency of preterm labour in non-diabetic women.

- The incidence of primary caesarian section among GDM ranged from 13.4% to 18.4%and repeat section in GDM is around 16.5%. The increased incidence nowadays may be due to quick option for caeserean section, when there is least problem.

ON THE FOETUS

- Hypoglycaemia is one of the common causes of perinatal morbidity. It is defined as blood sugar level less than 35 mg %. About50%of the hypoglycemic babies may remain asymptomatic. The factor mainly protective against foetal hypoglycemia is the optional control of maternal hyperglycemia especially during the third trimster and during labour. It has been shown that a mean maternal plasma glucose>105 mg/dl during the last four hours of labour in a diabetic mother leads to an higher incidence of neonatal hypoglycemia.

- About 25% of the infant of diabetic mothers may present with serum calcium of <7 mg/dl and this may remain mostly asymptomatic and is usually detectable during the 2^{nd} and 3^{rd} day of birth. Hypomagnesemia may coexist and may require correction.

- Respiratory distress syndrome [RDS] occurs in about 5% of the infant of diabetic mothers and it is seen equally in gestational diabetes mellitus. Again a strict glycamic control reduces the incidence of RDS.

- Polycythemia is relatively common in infant of diabetic mother. The

hyperviscosity due to Polycythemia may induce congestive heart failure and vascular thrombosis accounting for the increased risk of renal vein thrombosis in these infants.

- Hyperbilirubinemia, the common abnormality is due to increased bilirubin, production and decreased life span of the RBCs with glycosylated cell membranes. Hepatic conjugation of bilirubin may be impaired due to an immature liver.

FOETAL PROBLEMS ASSOCIATED WITH MATERNAL HYPERGLYCEMIA

First Trimester	Second Trimester	Third Trimester
Malformations Growth retardation Foetal wastage	Hypertrophy Cardiomyopathy Polyhydraminos Placental insufficiency Pre-eclampsia Foetal loss Low IQ	Hypoglycemia Hypocalcaemia Hyperbilirubinemia Respiratory –distress Syndrome Macrosomia Hypomagnesemia Intrauterine death

FOETAL HYPERINSULISM

Foetal hyperinsulism in the foetus is called Diabetic Foetopathy.According to Pedersen hypothesis; foetal hyperinsulinism is the major cause for adverse neonatal outcome. Insulin level in the cord blood of < 20microU /ml were

considered normal. Neonates with cord blood insulin levels >20microU/ ml represents a continuum of increasing diabetogenic fetopathy. Neonates with cord blood insulin < 20microU/ml as metabolically healthy, those with 20 – 50 microU/ml as having mild fetopathy, and those with >50microU/ml as having marked fetopathy (Early Hum Dev 1998 July).

Hence based on the above data this study was designed to screen pregnant women universally for GDM using 75 g OGTT. Of the diagnosed patients treatment with Insulin or glibenclamide was assigned randomly according to treatment protocol. HbA1c measured in all cases. They were followed till confinement and pregnancy outcome recorded.

CHAPTER - 3

AIM OF STUDY

To evaluate the safety and efficacy of Glibenclamide in comparison with Insulin for the treatment of Gestational diabetes mellitus in Indian population.

The Primary end point is to attain adequate glycaemic control.

Secondary end point is maternal and neonal outcome.

CHAPTER – 4

MATERIALS AND METHODS

The study "Comparison of Insulin and Glibenclamide in gestational diabetes mellitus" carried out in Govt RSRM Lying –in Hospital during the period from March 2005 to February 2006 with the concurrence of the ethical committee.

About 250 patients attending the antenatal clinic were included in screening for Gestational diabetes mellitus. The patients were selected randomly and belonged to gestational age between 11 to 33 weeks. At the first visit the patients were counseled for screening and asked to come after three days of unrestricted diet in a fasting state (8-10 hrs of overnight fasting) for a 75 gm oral glucose tolerance test.

Two samples of about 2cc blood were taken from each patient in fasting and two hours after a load of 75 gm of glucose in 200 ml of water. These samples were analysed by a semi automatic analyzer in the laboratory.

Patients were diagnosed as Gestational diabetes mellitus if fasting plasma glucose more than or equal to 95 mg /dl and or 2 hr PPGmore than or equal to 140 mg /dl. Among the 250 patients 35 had GDM according to the above

criteria.

Out of these, 5 patients did not give consent to get included in the study. In the remaining 30 patients, 15 patients were put on Insulin therapy and 15 patients were put on tablet Glibenclamide after getting an informed from the patient explaining the nature of the study. These women were randomly assigned to receive Insulin or Glibenclamide according to the treatment protocol. At the institution of treatment a detailed obstetric, family history and thorough clinical examination done. The incidence of GDM in the study was 14 %.

All the pregnant women included in the study were advised standard nutritional instruction for three meals and three snacks daily. Adherence to the dietary regimen was evaluated and reinforced at each visits to the clinic. The diet was designed to provide 25 kcal/kg of body weight for the obese women (BMI>27) and 35 kcal/kg (BMI<27) for the non-obese women with 40-45 % of the calories from carbohydrate.

In the women assigned to receive Insulin, it is started at a lower dose of 6units and a maximum of 55 units was used in the study. The dose was adjusted according to the glycaemic status. In the glibenclamide group the

starting was 0.625 mg orally, gradually increasing the dose and a maximum of 2.5 mg was used in the study to achieve adequate glycaemic control. The patients were instructed to come every 15 days for glycaemic profile. The aim was to keep fasting plasma glucose below 90 mg/dl and postprandial plasma glucose below 120 mg/dl and mean plasma glucose kept at 105 mg/dl measured at any time of the day. HbA1c was measured at the start of treatment and once again after delivery of baby. At each visit the patient undergoes detailed general and obstetric examination

Gestational age was determined on the basis of menstrual history and early USG if available. Ultrasound performed at 22, 28, 32 and 36 weeks to rule out macrosomia.

At delivery the neonatal team evaluated all neonates. Macrosomia is defined as birth weight greater than or equal to 3.5 kg. Neonate blood sugar and cord blood insulin level analyzed. Hypoglycaemia is defined as plasma glucose of the neonate below 35 mg /dl. Cord blood insulin is considered to be abnormal if it is more than 20 mIu /ml. Serum bilirubin was measured in babies when there was clinical evidence of jaundice and the babies were given phototherapy as needed.

INCLUSION CRITERIA

Women with gestational age between 11-33 weeks and who were willing to deliver at RSRM hospital

EXCLUSION CRITERIA

1. Women with gestational age less than 11 weeks and more than 33 weeks.

2. Women not willing to have their delivery at RSRM.

CHAPTER – 5

RESULTS

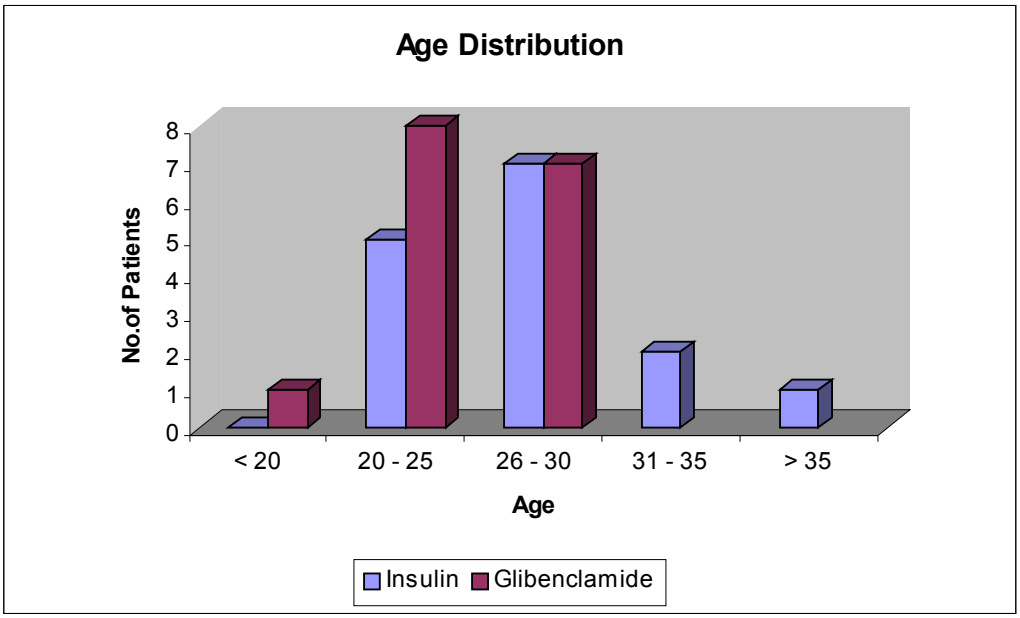
About 250 AN women attending the AN clinic were screened for GDM randomly with 75 gm OGTT. They were diagnosed as GDM if fasting plasma glucose more than or equal to 95 mg /dl and or 2 hr post glucose more than or equal to 140 mg /dl. 15 patients were put on insulin and 15 patients on glibenclamide according to treatment protocol. 2 patients were lost in followup in the glibenclamide group.

The demographic details were summarized in the table-I

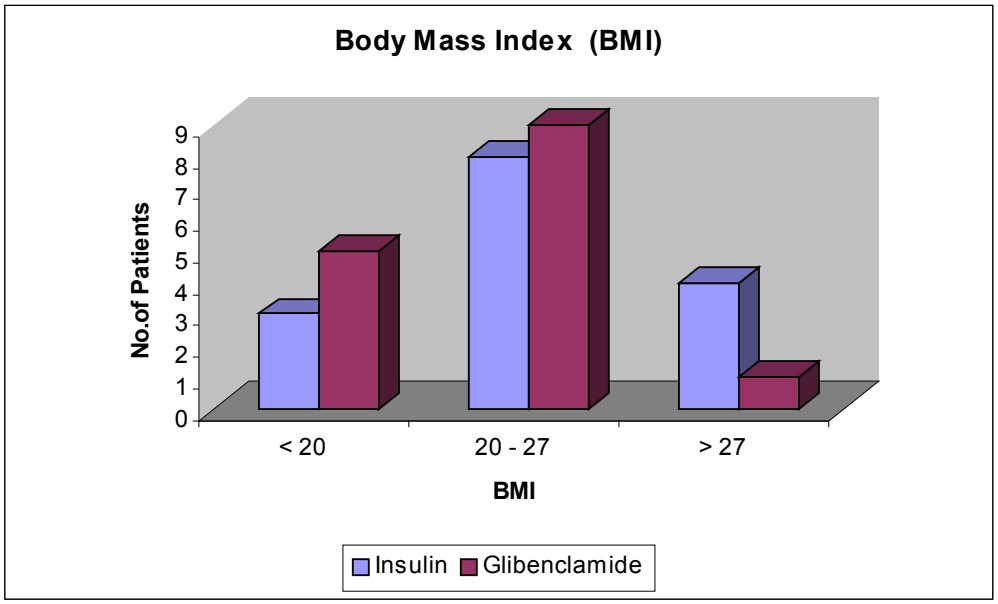
TABLE - I

	Group-I (Insulin) (N=15)	**Group-II (Glibenclamide) (N=15)**
Age	27.87 ± 5.0	24.7 ± 3.6
Pre-pregnancy wt	59.3 ± 11.5	49.9 ± 10.9
BMI	25.2 ± 4.6	21.8 ± 3.54
GA at entry into study	24.3 ± 5.23	23.5 ± 8.43

The demographic profile was comparable in both insulin and glibenclamide group.



Maximum No.of patients in both insulin and glibenclamide group are in the age group between 20 and 30 years.



Maximum No.of patients in both insulin and glibenclamide group have

BMI between 22 to 27.

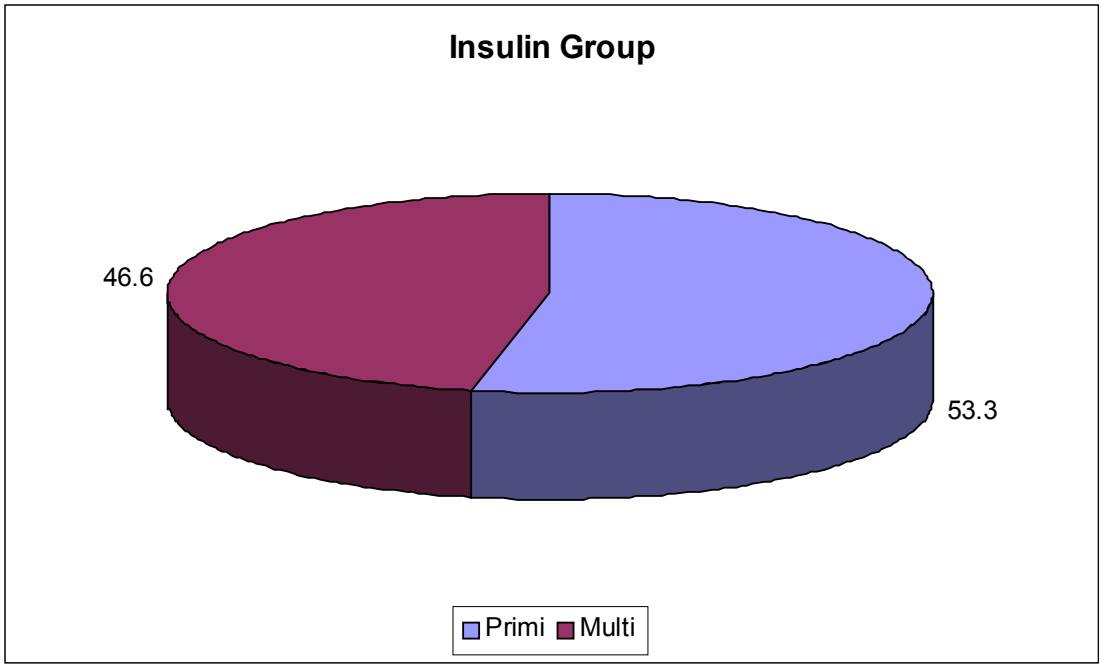
The gravidity distribution is given in table II

TABLE - II

Gravidity	Group-I (Insulin) (N=15)	Group-II (Glibenclamide) (N=15)
Primi	8 (53.3 %)	8 (53.3 %)
Multi	7 (46.6 %)	7 (46.6 %)

There was equal distribution of primi and multi gravida in both insulin and glibenclamide group.

GRAVIDITY DISTRIBUTION



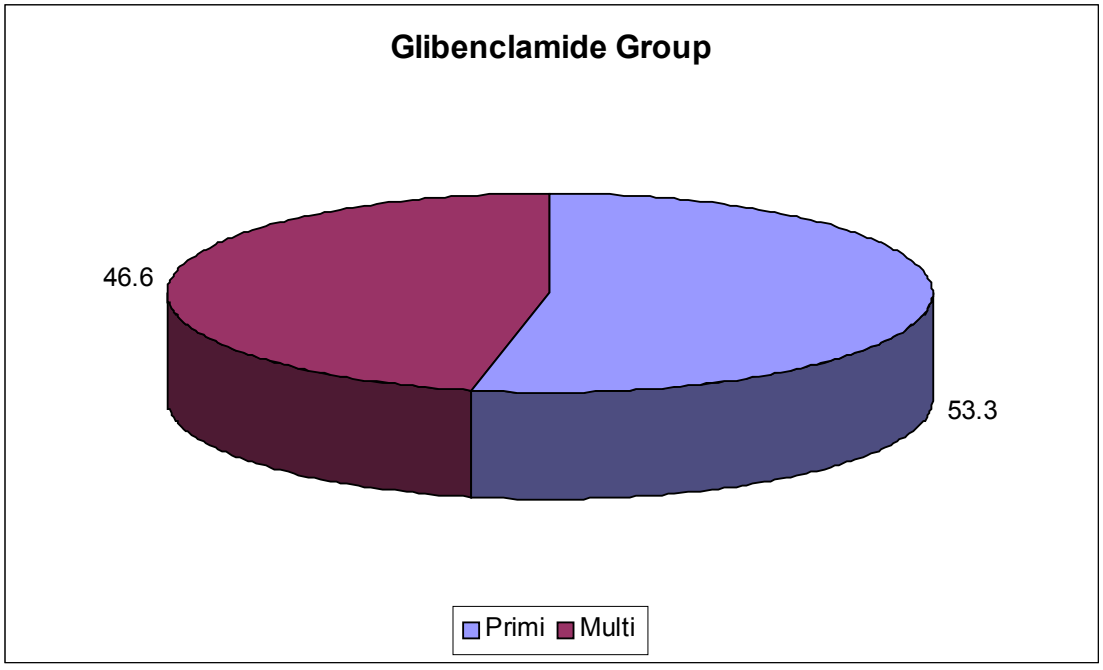


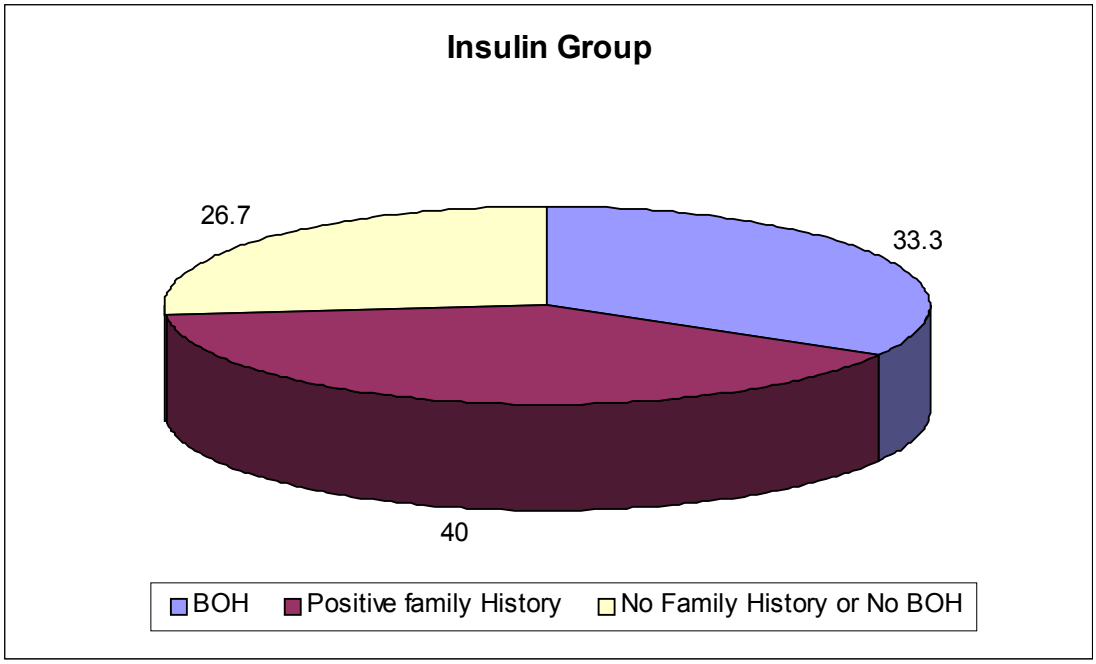
Table-III shows distribution of patient with positive family history of diabetes and with bad obstetric History.

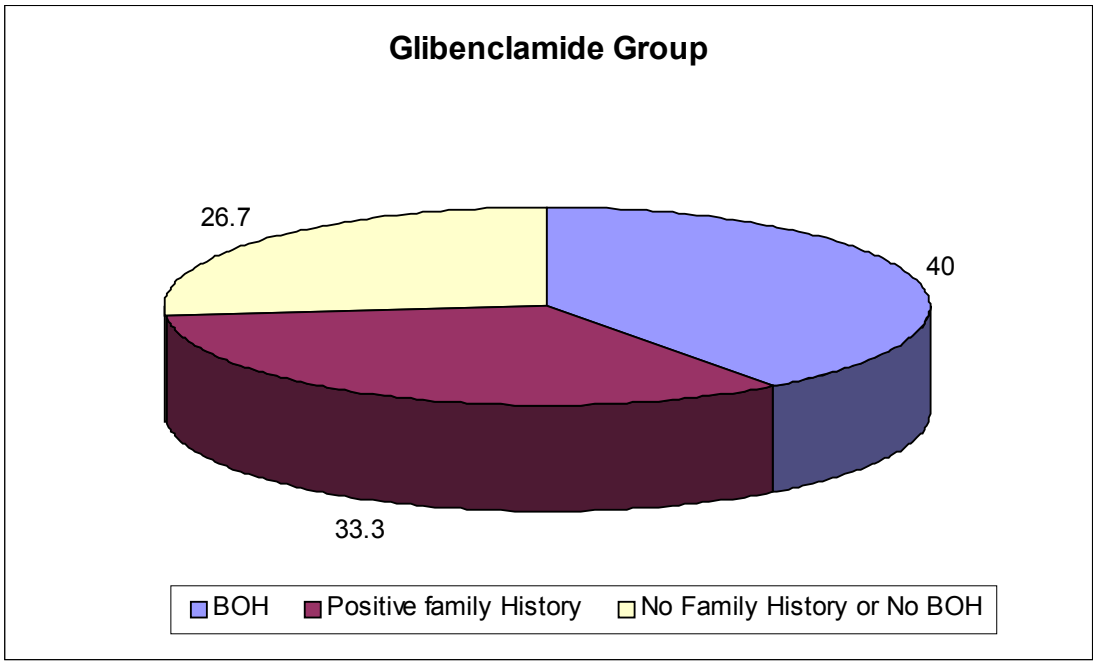
TABLE - III

	Group-I (Insulin) (N=15)	**Group-II (Glibenclamide) (N=15)**
BOH	5 (33.3 %)	6 (40.0 %)
Positive family history	6 (40.0 %)	5 (33.3 %)

There was almost equal distribution of antenatal women with bad obstetric history and positive family history of diabetes in both insulin and glibenclamide group.

BOH & FAMILY HISTORY





The screening plasma sugar values are summarized in the following table-IV

TABLE – IV

	Group-I (Insulin) (N=15)	**Group-II (Glibenclamide) (N=15)**	**'P' Value**
Fasting Plasma Glucose	90.07 ± 22.1	75.73 ± 23	0.072
2 hr Post Glucose Plasma Glucose	177.8 ± 28.4	173.2 ± 25.35	0.65

There was 6 patients in insulin group and 2 patients in the glibenclamide group with fasting plasma glucose more than or equal to 95 mg / dl (fasting hyperglycaemia).

The screened patients were selected randomly for treatment with insulin or glibenclamide.. The glycaemic status of the women during the course of treatment is summarized in table-V.

TABLE – V

	Group-I (Insulin) (N=15)	**Group-II (Glibenclamide) (N=15)**	**'P' Value**
Fasting Plasma Glucose	68.53 ± 13.5	62.27 ± 7	0.96
2 hr Post	98.6 ± 10.1	95.9 ± 6.1	0.44

Prandial Plasma Glucose			

The aim of treatment was to keep fasting plasma glucose below 90 mg / dl and Post Prandial plasma glucose below 120 mg / dl and mean plasma glucose 105 mg / dl measured at any time of the day. Adequate glycaemic control was achieved in both insulin and glibenclamide group. A maximum dose of 2.5 mg of glibenclamide was needed in the study to achieve desired glycaemic level.

Pre-treatment HbA1C as compared with post –treatment HbA1c (Table-VI).

TABLE - VI

	Group-I (Insulin) (N=15)	**Group-II (Glibenclamide) (N=15)**	**'P' Value**
Pre – Treatment HbA1c	5.5 ± 0.89	5.1 ± 0.46	0.45
Post Treatment HbA1c	5.5±0.56	5.38±0.31	0.60

Both pre-treatment and Post –treatment HbA1c values were similar in both the treatment groups.The values were not significant and it also indicates HbA1c may not be very useful in GDM because of lesser degree of hypoglycaemia in GDM.

The patients were followed upto delivery and the Pregnancy outcome details recorded. The pregnancy outcome details were illustrated in table-VII.

TABLE - VII, NEONATAL OUT COME

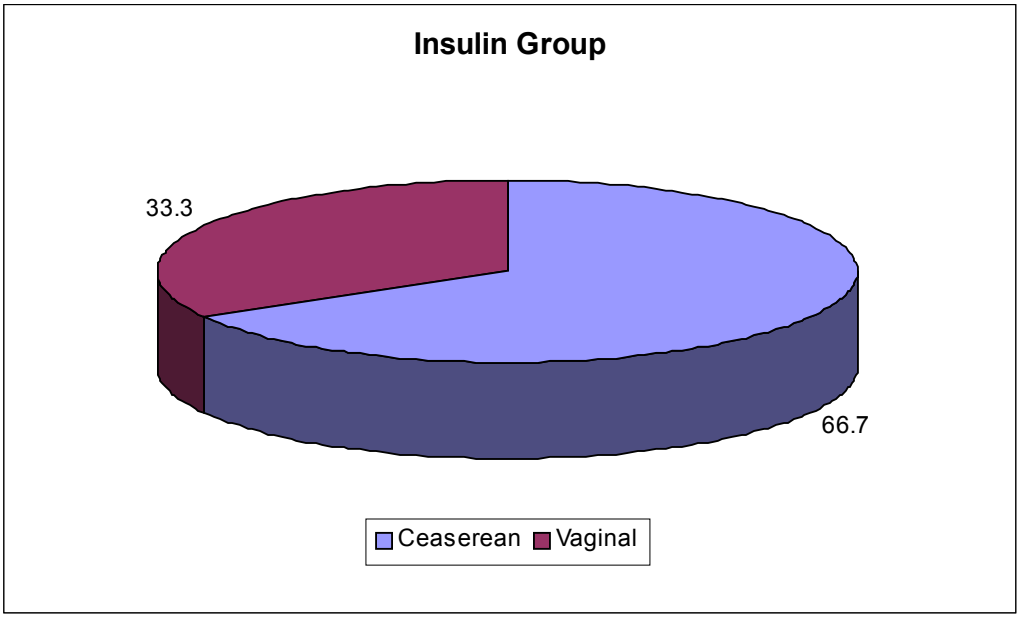
	Group-I (Insulin) (N = 15)	**Group-II (Glibenclamide) (N = 13)**	**'P' Value**
Birth weight	2.88 ± 0.45	2.56 ± 0.84	0.23
New born Plasma Glucose	72.87 ± 28.4	69.1 ± 14.45	0.78
Cord Blood Insulin	5.24 ± 2.7	4.88 ± 4.9	0.89
NICU Admission for photo-theraphy	3(20%)	1(7.7%)	-

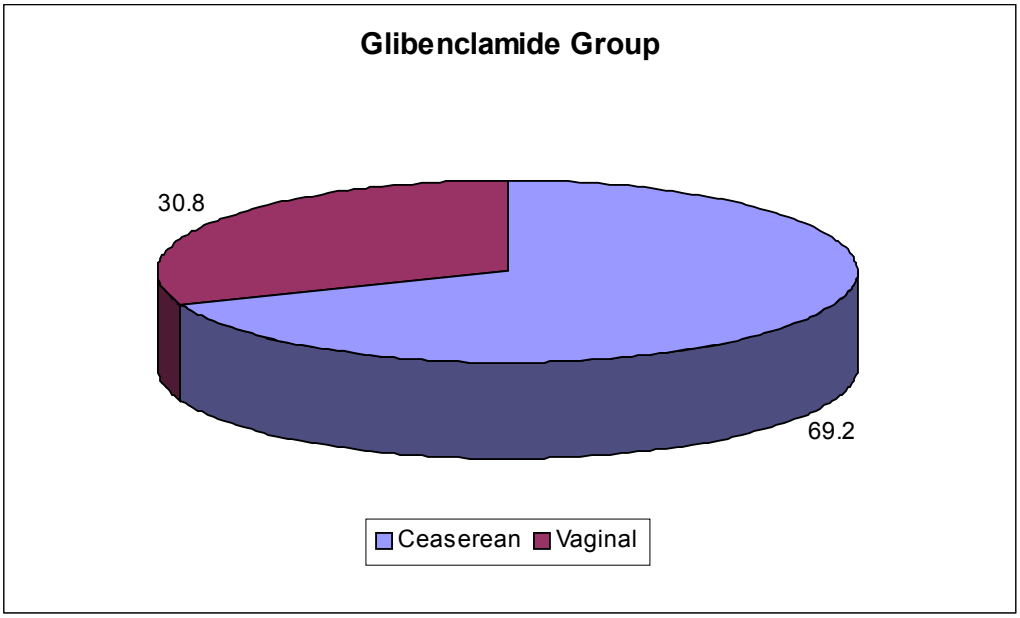
TABLE - VIII, MATERNAL OUT COME

	Group-I (Insulin) (N = 15)	**Group-II (Glibenclamide) (N = 13)**
PIH	2 (13.3%)	1 (7.7%)
Polyhydraminos	Nil	Nil
Retinopathy	Nil	Nil
Caesarean Deliveries	10 (66.7%)	9 (69.2%)

The pregnancy outcome were similar in both the groups. Except one patient in glibenclamide group had second trimester abortion probably due to late detection and one patient in insulin group delivered a macrosomic baby (3.5 kg). Hypoglycaemia was not detected in any of the babies in both the groups. Three neonates in insulin group and one neonate in glibenclamide group needed phototheraphy for clinical jaundice for 1 to 2 days. Cord blood insulin was in normal range in both the groups indicating absence of hyperinsulinemia. There was no case of congenital anomaly in the study. Post delivery HbA1c was normal in both groups indicating good glycaemic control during treatment. Incidence of PIH and cesarean delivery was same in insulin and glibenclamide group.

CEASEREAN Vs VAGINAL





Fasting and post prandial plasma glucose was taken in all patients before discharge from the hospital. This is summarized in table-VII.

TABLE - IX

	Group-I (Insulin)	**Group-II (Glibenclamide)**	**'P' Value**
Fasting Plasma Glucose	68.07 ± 16.9	66.27 ± 7.0	0.53
2 hr Post Prandial Plasma Glucose	95.47 ± 10.97	95.9 ± 6.1	0.89

Post delivery fasting and post prandial plasma glucose was normal in all patients.There were no significant differences between the two groups in any of the characteristics depicted in all the tables by student's t- test, suggesting both the drugs are equally effective.

CHAPTER – 6

DISCUSSION

The present study comparing the effects of insulin and glibenclamide in GDM had 15 patients in insulin group and 15 patients in glibenclamide group. 2 patients in glibenclamide group were lost in the follow up.

The demographic details in the present study compared with the study done by Langer et al comparing 203 patients in insulin group and 201 patients in glibenclamide group.

TABLE-I DEMOGRAPHIC PROFILE

	Insulin Group			**Glibenclamide Group**		
	Age	**BMI > 27**	**GA at Entry**	**Age**	**BMI > 27**	**GA at Entry**
Present Study	27.87± 5.0	4 (26.6 %)	24.3±5 .23	24.70± 3.6	1 (6.67 %)	23.5±8. 43
Langer et al Study	30.0±6 .0	132 (65%)	25.0±7 .0	29.0±7 .0	141 (70%)	24.0±7. 0

The age distribution in present study is slightly lower but comparable with Langer et al one. The slightly lower age distribution in present study may be due to younger age at marriage in our society. More non-obese patients with BMI <27 were included in present study as compared to the study done by Langer et al in which more obese patients were included in the study in both insulin (65%) and glibenclamide (70%) group. Gestational age at entry into study was similar and comparable in both present study and study by Langer et al.

TABLE-II GLYCAEMIC STATUS DURING TREATMENT

	Insulin Group		**Glibenclamide Group**	
	Fasting Plasma Glucose	**Postprandial Plasma Glucose**	**Fasting Plasma Glucose**	**Postprandial Plasma Glucose**
Present Study	68.53±13.5	98.6±10.1	62.27±7.0	95.9±6.1
Langer et al Study	98.0±13.0	113±22	96.0±16.0	112.0±15.0

Adequate glycaemic control was achieved in both insulin and glibenclamide group in the present study and no patient was switched over to insulin because of poor glycaemic control. In Langer et al study except 8 patients (4%) who were switched over to insulin owing to poor glycaemic control

with maximum dose of glibenclamide (20 mg) other patients attained good glycaemic control in both the groups. The blood sugar values of patients of Langer et al study given in the table was measured by them at home which had a strong association with the blood sugar values taken during clinic visits. The mean plasma glucose concentration measured during clinic visits was 102 +24mg /dl in glibenclamide group and 99+22mg/dl in the insulin group.

Pre-pregnant HbA1c in present study as compared with Langer et al study.

TABLE - III PRE-PREGNANT HbA1c

	Insulin Group	**Glibenclamide Group**	**'P' Value**
Present Study	5.5±0.89	5.1±0.46	0.45
Langer et all Study	5.7±1.3	5.6±1.2	0.42

Pre –pregnant HbA1c were similar in both present study and Langer et al study and lie within normal range.

The neonatal outcome of present study compared with Langer et al study.

TABLE-IV NEONATAL OUT COME

	Insulin Group				Glibenclamide Group			
	Birth wt	**Cord blood insulin**	**Still birth**	**Neonatal death**	**Birth wt**	**Cord blood insulin**	**Still birth**	**Neonatal death**
Present Study	2.88± 0.45	5.24 ±2.7	0	0	2.56± 0.84	4.88 ±4.9	0	0
Langer et al Study	3.19± 0.59	15.0 ±2.1	1	1	3.25± 0.53	15.0 ±1.3	1	1

TABLE-V MATERNAL OUT COME

	Insulin Group		Glibenclamide Group	
	Pre-Eclampsia	Caesarian	Pre-Eclampsia	Caesarian
Present Study	13.3 %	66.7 %	7.7 %	69.2 %
Langer et al Study	6.0 %	24.0 %	6.0 %	23.0 %

There was no case of still birth or neonatal death in the present study

compared to that of Langer et al one where there was one case of still birth and neonatal death in each insulin and glibenclamide group.There was one case of macrosomia in the present study in the insulin group (6.6%) and no case of macrosomia in the glibenclamide group. In Langer et all study the incidence of macrosomia was 8% in glibenclamide group and 6% in the insulin group. Cord blood insulin was in normal range in both studies indicating absence of hyperinsulinemia.The incidence of preeclampsia was 13.3% in insulin group and 7.7%in glibenclamide group in present study compared to Langer et al study where incidence of preeclampsia was 6% in both groups.The cesarean section rate was 66.7%in insulin group and 69.2% in glibenclamide group in the present study compared to Langer et al study where it was 24% and 23% respectively.

In another study by Kremer et al using glyburide for the treatment of gestational diabetes. 73 patients were treated with glyburide of which 59 achieved satisfactory control (80 .8%).In the present study all patients achieved good glycaemic control . 19% had macrosomic infants in kremer et al study , in the present study there was no case of macrosomia in glibenclamide group.

In another study by Hellmuth et al study where OHA was used in 118

patients the neonatal and maternal outcome was similar in both insulin and glibenclamide group as in present study.

In another study by Lim J M , Tayob Y, O'Brien PM, Shaw RW where 33 patients were put on glibenclamide and 21 on insulin . The maternal and foetal outcome were not statistically different between the two treatment groups in the study as in the present study.

There were only few studies using glibenclamide in GDM and therefore scant information on its efficacy. More studies are yet to come before its use in clinical practice.

CHAPTER – 7

SUMMARY

- About 250 women attending the AN clinic were screened randomly for gestational diabetes by using 75 g OGTT and diagnosed as GDM if fasting plasma glucose more than or equal to 95 mg % and or postprandial plasma glucose more than or equal to 140 mg %.

- Based on the above criteria 35 patients were diagnosed as GDM. 5 patients did not give consent to get included in the study . Of the remaining, 15 patients were put on insulin and 15 patients on glibenclamide .They were asked to attend diabetic clinic every 15 days for plasma sugar monitoring.

- These patients were followed throughout pregnancy and their pregnancy details recorded.The maternal and neonatal outcome was similar in both insulin and glibenclamide group except one 2^{nd} trimester abortion in glibenclamide group and delivery of one macrosomic baby in the insulin group.There was no case of congenital anomaly.

- Cord blood insulin and HbA1c assayed. Postdelivery plasma glucose taken in all cases before discharge and found to be in normal range.

CHAPTER – 8

CONCLUSION

In the study, the degree of glycaemic control and the perinatal outcomes were essentially the same for those treated with glibenclamide and insulin, except one bad outcome in glibenclamide group who had II trimester abortion probably due do late detection and one baby who was macrosomic (3.5 kg) in the Insulin group.The lack of differences between the infants born to mother in the two treatment groups corroborated the results in the mother.

Maternal hyperglycaemia in GDM is translated to the foetus resulting in foetal hyperglycaemia which is more deleterious to the foetus than the drug effect used in the treatment of GDM. Moreover glibenclamide does not cross the placenta due to its property of extensive protein binding ,short half life ,and acting as a substrate for P-glycoprotein and inhibiting it.

Hence the conclusion of the study is that glibenclamide may be a safe and efficient alternative therapy to Insulin in the treatment of GDM. Since the sample size is small, more studies are needed to substantiate this finding.

STUDY PROFORMA

A GENERAL

Name :

Age : *Education :*

Address & Telephone No :

Date of inclusion into study :

LMP: *EDD:*

Gestational Age at the time of inclusion into study:

B OBSTETRIC HISTORY

Grivida	Para	Abortion	Stillbirth

FAMILY HISTORY

Father Y/N : *Mother Y/N :*

Siblings Y/N : *1st degree relatives Y/N :*

GE :

Anaemia Y/N :

Pedal Edema Y/N :

Acanthosis nigricans Y/N :

BP :

Height : *Weight*

Pre-pregnancy weight :

BMI (calculated from the pre-pregnancy weight) :

C. ASSOCIATED PROBLEMS IN PREVIOUS PREGNANCIED

Pregnancy	Delivery Y/N	If no was it wasted	**Maternal complications**						
			GDM / IGT	Pre-Eclamsia	PCOD	Endocrine disorders	Proteinuria	Rx	Other information

D. PREVIOUS PREGNANCIES OUTCOME :

Pregnancy	Date of delivery	Details of delivery			Sex of child	Details of child		
		Normal	Assisted	Caesarean		Birth weight	Congenital abnormalities Y/N	Other complications Y/N If yes, details

E. SCREENING DATAILS

Date of Screening :

Week of gestation :

FPG :

2 Hr PPG :

OTHER INV :

Microalbuminuria :

Retinopathy :

Others :

F. TREATMENT SCHEDULE :

Visit log	Date of visit	Gest week	Plasma glucose	Glibenclamide (in mg) / Insulin

G. USG FINDINGS (include fetal abdominal circumference)

22 weeks	28 weeks	32 weeks	36 weeks

H. OUTCOME OF PRESENT PREGNANCY

Delivered : Y/N

If no was it wasted :

If delivered :

D.O.D :

Sex of the child :

Mode of delivery : Spontaneous ( ) Induction ( ) Caesarean ( )

Weight :

Height :

Apgar :

New born Infants blood glucose :

I. MATERNAL COMPLICATIONS :

Proteinuria : Y/N

Retinopathy : Y/N

Others :

J. NEONATAL COMPLICATIONS :

Congential abnormality Y/N if yes specify :

Neonatal Hypoglycemia : (Y/N)

Shoulder Dystocia : (Y/N)

Any other Information :

ABBREVIATIONS

ATP	-	Adenosine Triphosphate
BMI	-	Body Mass Index
BOH	-	Bad obstetric History
BP	-	Blood Pressure
EDD	-	Expected Date of Delivery
GA	-	Gestational Age
GDM	-	Gestational Diabetes Mellitus
HbA1c	-	Glycosylated Haemoglobin
HPL	-	Human placental lactogen
LMP	-	Last Menstrual period
NBPG	-	New Born plasma glucose
NDDG	-	National Diabetes Data Group
NICU	-	Neonatal intensive care unit
OGCT	-	Oral Glucose Challenge Test
OGTT	-	Oral Glucose Tolerance Test
OHA	-	Oral Hypoglycaemic Agents
PG	-	Plasma Glucose
SD	-	Standard deviation
USG	-	Ultrasonogram
WHO	-	World health organization